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10/534,079	11/14/2005	Mark Theodoor Verhaar	0470-051409	5293

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EXAMINER	
TOWNSLEY, SARA ELIZABETH	

ART UNIT	PAPER NUMBER
1613	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/534,079	Applicant(s) VERHAAR ET AL.	
	Examiner SARA E. CLARK	Art Unit 1613	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 September 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *32-34 and 36-73* is/are pending in the application.

4a) Of the above claim(s) *49-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-34 and 36-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

FINAL REJECTION

Receipt is acknowledged of Applicants' Amendments and Remarks, filed 9/27/2010.

Claims 1-31 and 35 have been cancelled.

Claims 32, 36, 41, and 42 have been amended and incorporate no new matter.

No new claims have been added.

Claims 49-73 stand withdrawn as drawn to non-elected inventions.

Thus, claims 32-34 and 36-48 now represent all claims currently pending and under consideration.

INFORMATION DISCLOSURE STATEMENT

No new Information Disclosure Statements (IDS) have been submitted.

WITHDRAWN OBJECTIONS/REJECTIONS

Objections

Due to the cancellation of claim 35, the objection to claim 35 is rendered moot and is withdrawn.

Rejections under 35 USC §112, Second Paragraph

Due to the amendments to the claims, the rejection of claims 32-48 under 35 USC 112, second paragraph, for indefiniteness relating to “protecting group C,” is withdrawn.

Due to the amendments to the claims, the rejection of claims 41-43 under 35 USC 112, second paragraph, for indefiniteness relating to “PVP,” is withdrawn.

MAINTAINED REJECTIONS

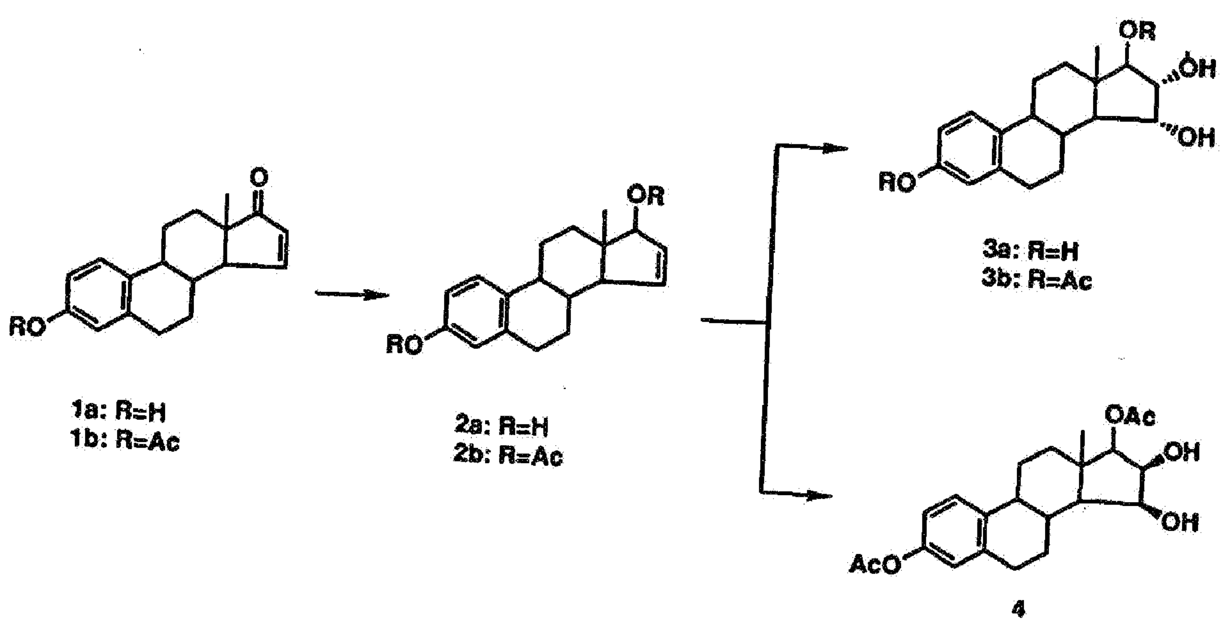
The following rejection is maintained from the previous Office Action dated 5/25/2010, on the ground that the references cited therein continue to read on the limitations of the amended claims.

Rejections under 35 USC §103

A. Claims 32-34, 36-38, 40, and 46-48 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Suzuki et al. (Steroids 60, 277-284 (1995)) in view of Poirier et al. (Tetrahedron 47(37), 7751-66 (1991) (both provided by Applicant on the IDS dated 1/9/2006), as evidenced by Greene's Protective Groups in Organic Synthesis 3E (1999).

Suzuki et al. disclose a process for the preparation of estra-1,3,5(10)-trien-3,15α,16α,17β-tetraol (a.k.a. estetrol or E4) comprising:

- Starting with estrone, compound (1a), 15-dehydroestrone, is synthesized in five steps;
- Protection of the 3-OH by conversion to 3-OAc to give compound (1b), followed by reduction with $LiAlH_4$ to give compound (2a), 15-dehydroestradiol;
- Protection of the 17-OH by conversion to 17-OAc to give compound (2b);
- Oxidation with OsO_4 to give compound (3b), estra-1,3,5(10)-trien-3,15α,16α,17β-tetraol diacetate (with –OAc protecting groups at the 3 and 17 positions) in 46% yield; (see scheme 1; p. 281, right column, first full paragraph); and
- Deprotection of 3-OAc and 17β-OAc by extraction from ethyl acetate to give compound (3a), estetrol (see p. 278, right column).



Thus, Suzuki et al. disclose a process for

(1) converting estrone into 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one, wherein A is a protecting group (compound 1b);

(2) reducing the 17-keto group to 3-A-oxy-estra-1,3,5(10),15-tetraen-17β-ol (compound 2a);

(3) protecting the 17-OH group to give 3-A-oxy-17-Cp-oxy-estra-1,3,5(10),15-tetraene, wherein Cp is a protecting group (compound 2b);

(4) oxidizing the carbon-carbon double bond of ring D (C_{15}=C_{16}) to give 3,17-diprotected estetrol (compound 3b);

(5) and removing the protecting groups A and Cp to give estetrol,

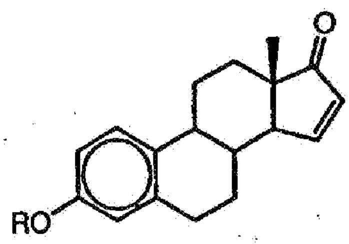
as recited by steps 1, 2, 3, 4, and 5 of claim 32.

Suzuki et al. disclose acetyl as the 17-OH protecting group Cp, as recited by claims 32, 35, and 36; reduction of the carbonyl (17-keto) group with a metal hydride compound ($LiAlH_4$), as recited by claims 37 and 38; and oxidation of the Δ^{15} double bond with OsO_4, as recited by claim 40.

However, Suzuki et al. do not disclose a 3-OH protecting group A which is a C_1-C_5 alkyl group or a C_7-C_{12} benzylic group; or that the 3-OH protecting group A is removed prior to removing the 17-OH protecting group Cp, as recited by claim 32.

Poirier et al. disclose the conversion of estrone to estra-1,3,5(10),15-tetraen-17-one according to well-known methodology (p. 7758), followed by protection of the 3-OH group with benzyl or methyl to give 3-benzyloxy-estra-1,3,5(10),15-tetraen-17-one

(compound 8) or 3-methoxy-estra-1,3,5(10),15-tetraen-17-one (compound 9), respectively (p. 7758; scheme 1).



8 R=Bn
9 R=CH_3

Compound (8) corresponds to the claimed compound wherein protecting group A is a benzyl group, as recited by claims 32-34, and compound (9) corresponds to the claimed compound wherein protecting group A is a methyl (C_1-C_5 alkyl) group, as recited by claim 32.

In addition, Poirier et al. disclose the deprotection of the 3-OH protecting group A, corresponding to step 5 as recited by claim 32. Where the 3-OH protecting group A is benzyl, it can be removed by catalytic hydrogenation at atmospheric pressure using hydrogen gas with a palladium/carbon (Pd/C) catalyst (scheme 1, step (f); p. 7755), as recited by claims 46 and 47. Where the 3-OH protecting group A is methyl, it can be removed by using BBr_3 in dichloromethane (scheme 1, step (g)), as recited by claim 48.

Thus, Poirier et al. teach protection of the 3-OH group of D-ring modified estrogens with a benzyl group or with a methyl group, and subsequent deprotection. The 3-O-benzyl- or 3-O-methyl-protected compounds (8) and (9) are disclosed as starting materials for synthesis of C_{15} alkylated steroids, which Poirier et al. carried out by the use of copper-catalyzed conjugate addition of Grignard reagent (p. 7752).

One of ordinary skill in the chemical arts would have been motivated to modify the 3-O-acetate (ester) protecting group disclosed by Suzuki et al. by protecting the 3-OH group with O-methyl or O-benzyl ethers, as taught by Poirier et al., because the following step, reduction with $LiAlH_4$, would cleave the acetate protecting group to yield the unprotected 3-OH (conversion of compound 1b to compound 2a), and requires re-protecting the 3-OH group in the next step (conversion of compound 2a to compound 2b) to survive the reaction conditions of the steps that follow. $LiAlH_4$ is known to reduce esters (such as –OAc) to primary alcohols, while methyl or benzyl 3-OH protecting groups (ethers) would not be reduced by $LiAlH_4$ (see, e.g., attached chart showing that methyl ether and benzyl ether (hydroxyl protecting groups 1 and 26) have low reactivity, i.e., are stable, in the presence of hydride reducing agents including $LiAlH_4$ and $NaBH_4$). Thus, methyl and benzyl ethers would be expected to function as effective 3-OH protecting groups that would obviate the need to subsequently repeat a hydroxyl-protecting step following the metal hydride reduction.

Finally, it is noted that Suzuki et al. disclose the simultaneous cleavage of the 3-OAc and 17-OAc protecting groups by alkaline hydrolysis (conversion of compound 3b to compound 3a, estetrol), rather than separate deprotection steps, namely deprotection of the 3-OH group prior to deprotection of the 17-OH group, as recited by claim 32. However, whereas the 3-OH and 17-OH protecting groups of Suzuki are identical (acetate), it is predictable that distinct deprotection steps may be necessary where the protecting groups are different, as required by the definitions of A and Cp as recited by claim 32. Further, the specification indicates that the order of the deprotection steps can

be reversed or performed simultaneously with no material change in the final product (WO04/41839, p. 20, lines 17-26). As recognized by MPEP §2144.04, citing *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946), selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results; see also *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (selection of any order of mixing ingredients is *prima facie* obvious).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the synthesis of estetrol from estrone as taught by Suzuki et al. by modifying the 3-OH protecting group from acetate to methyl or benzyl, as taught by Poirier et al. with a reasonable expectation of success, because doing so would eliminate the need to repeat the 3-OH protecting step, simplifying the process.

B. Claims 32-34, 36-40, and 46-48 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Suzuki et al. and Poirier et al. as evidenced by Greene (1999), as applied to claims 32-34, 36-38, 40, and 46-48 above, and further in view of Pearlman (USPN 4,739,078) as evidenced by Chemical Land data sheet for $LiAlH_4$.

As discussed above, **Suzuki et al**. (scheme 1) disclose a process for the synthesis of estetrol from estrone, comprising

(1) converting estrone into 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one, wherein A is a protecting group (compound 1b);

(2) reducing the 17-keto group to 3-A-oxy-estra-1,3,5(10),15-tetraen-17β-ol (compound 2a);

(3) protecting the 17-OH group to give 3-A-oxy-17-Cp-oxy-estra-1,3,5(10),15-tetraene, wherein Cp is a protecting group (compound 2b);

(4) oxidizing the carbon-carbon double bond of ring D (C_{15}=C_{16}) to give 3,17-diprotected estetrol (compound 3b);

(5) and removing the protecting groups A and Cp to give estetrol,

as recited by steps 1, 2, 3, 4, and 5 of claim 32.

Suzuki et al. disclose acetyl as the 17-OH protecting group Cp, as recited by claims 32, 35, and 36; reduction of the carbonyl (17-keto) group with a metal hydride compound ($LiAlH_4$), as recited by claims 37 and 38; and oxidation of the Δ^{15} double bond with OsO_4, as recited by claim 40.

Poirier et al. disclose the conversion of estrone to estra-1,3,5(10),15-tetraen-17-one according to well-known methodology (p. 7758), followed by protection of the 3-OH group with benzyl or methyl to give 3-benzyloxy-estra-1,3,5(10),15-tetraen-17-one (compound 8) or 3-methoxy-estra-1,3,5(10),15-tetraen-17-one (compound 9), respectively (p. 7758; scheme 1). Compound (8) corresponds to the claimed compound wherein protecting group A is a benzyl group, as recited by claims 32-34, and compound (9) corresponds to the claimed compound wherein protecting group A is a methyl (C_1-C_5 alkyl) group, as recited by claim 32.

In addition, Poirier et al. disclose the deprotection of the 3-OH protecting group A, corresponding to step 5 as recited by claim 32. Where the 3-OH protecting group A

is benzyl, it can be removed by catalytic hydrogenation at atmospheric pressure using hydrogen gas with a palladium/carbon (Pd/C) catalyst (scheme 1, step (f); p. 7755), as recited by claims 46 and 47. Where the 3-OH protecting group A is methyl, it can be removed by using BBr_3 in dichloromethane (scheme 1, step (g)), as recited by claim 48.

Thus, Poirier et al. teach the protection and deprotection of the 3-OH group of D-ring modified estrogens with a benzyl group or with a methyl group. The 3-O-benzyl- or 3-O-methyl-protected compounds (8) and (9) are disclosed as starting materials for synthesis of C_{15} alkylated steroids, which Poirier et al. carried out by the use of copper-catalyzed conjugate addition of Grignard reagent (p. 7752).

One of ordinary skill in the chemical arts would have been motivated to modify the 3-O-acetate (ester) protecting group disclosed by Suzuki et al. by protecting the 3-OH group with O-methyl or O-benzyl ethers, as taught by Poirier et al., because the following step, reduction with $LiAlH_4$, would cleave the acetate protecting group to yield the unprotected 3-OH (conversion of compound 1b to compound 2a), and requires re-protecting the 3-OH group in the next step (conversion of compound 2a to compound 2b) to survive the reaction conditions of the steps that follow. $LiAlH_4$ is known to reduce esters (such as –OAc) to primary alcohols, while methyl or benzyl 3-OH protecting groups (ethers) would not be reduced by $LiAlH_4$ (see, e.g., Greene, disclosing that methyl ether and benzyl ether (hydroxyl protecting groups 1 and 26) have low reactivity, i.e., are stable, in the presence of hydride reducing agents including $LiAlH_4$ and $NaBH_4$). Thus, methyl and benzyl ethers would be expected to function as effective 3-OH

protecting groups that would obviate the need to subsequently repeat a hydroxyl-protecting step following the metal hydride reduction.

It is noted that Suzuki et al. disclose the simultaneous cleavage of the 3-OAc and 17-OAc protecting groups by alkaline hydrolysis (conversion of compound 3b to compound 3a, estetrol), rather than separate deprotection steps, namely deprotection of the 3-OH group prior to deprotection of the 17-OH group, as recited by claim 32. However, whereas the 3-OH and 17-OH protecting groups of Suzuki are identical (acetate), it is predictable that distinct reagents for each deprotection step may be necessary where the protecting groups are different, as required by the definitions of A and Cp as recited by claim 32. Further, the specification indicates that the order of the deprotection steps can be reversed or performed simultaneously with no material change in the final product (WO04/41839, p. 20, lines 17-26). As recognized by MPEP §2144.04, citing *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946), selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results; see also *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (selection of any order of mixing ingredients is *prima facie* obvious).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the synthesis of estetrol from estrone as taught by Suzuki et al. by modifying the 3-OH protecting group from acetate to methyl or benzyl, as taught by Poirier et al. with a reasonable expectation of success, because doing so would eliminate the need to repeat the 3-OH protecting step, simplifying the process.

However, Suzuki et al. and Poirier et al. do not disclose reduction of the 17-keto group with $NaBH_4$ in combination with $CeCl_3$ hydrate ($NaBH_4/CeCl_3$), as recited by claim 39.

Pearlman et al. disclose a method of stereoselectively reducing carbonyl groups of biologically important prostaglandin intermediates (abstract), in particular under Luche conditions (that is, by the use of $NaBH_4/CeCl_3$) (col. 4, lines 13-14 and 26-27; Example 1; Table 1). A prostaglandin enone is treated with a borohydride salt (e.g., sodium borohydride) and a lanthanide salt (e.g., cerium trichloride) in an inert solvent at a low temperature to give a high yield of the corresponding 15α-hydroxy epimer (col. 6, line 67 to col. 7, line 5).

In addition, Pearlman et al. disclose that suitable protecting groups for other functional groups on the molecule include any group capable of surviving the conditions of the reaction, to include a group which replaces a hydroxy hydrogen (col. 4, lines 32-35), such as acyl or benzyl (col. 5, lines 4-10). As evidenced by, for example, the attached Chemical Land data sheet, $LiAlH_4$ is a powerful reducing agent which can be used to reduce esters, but $NaBH_4$ is a milder reducing agent that does not react with esters. Thus, Pearlman discloses that acyl or benzyl protecting groups can be used equivalently where $NaBH_4$ is the reducing agent, buttressing the motivation provided by Poirier et al. to modify the 3-O-acetyl protecting group of Suzuki et al. to 3-O-benzyl.

One of ordinary skill in the chemical arts would have been motivated to modify the reduction reagent of Suzuki et al. ($LiAlH_4$) by employing Luche reduction conditions ($NaBH_4/CeCl_3$) to reduce the 17-keto group of 3-A-oxy-estra-1,3,5(10),15-tetraen-17-

one, because ring D is an enone (Δ^{15}, 17-keto), and Pearlman teaches that $NaBH_4$ in $CeCl_3$ is effective for the stereoselective reduction of enone carbonyl groups to yield predominantly one epimer over the other (see Table IV). $NaBH_4$ in $CeCl_3$ would have been predicted to selectively convert the 17-carbonyl group to 17β-hydroxy because (1) the C_{18} methyl group is in β-orientation, which would be expected to create steric hindrance above the plane of the D ring (flattened due to the Δ^{15} double bond), so that the metal hydride would preferentially add hydrogen to the α-face, placing the reduced hydroxyl group in β-orientation; and (2) $CeCl_3$ enhances the stereoselectivity of the reaction by coordinating with the solvent (such as methanol).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the synthesis of estetrol disclosed by Suzuki et al., as modified by Poirier et al., by employing $NaBH_4$ in $CeCl_3$ rather than $LiAlH_4$ as the 17-keto metal hydride reducing agent, as taught by Pearlman, with a reasonable expectation of success, because (1) the Luche reduction was known to be effective in the stereoselective reduction of biologically important enone intermediates with higher yields of the desired epimer, and (2) Pearlman teaches that benzyl is a suitable hydroxyl-protecting group capable of withstanding the reaction conditions.

C. Claims 32-34, 36-38 and 40-48 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Suzuki et al. and Poirier et al. as evidenced by Greene (1999), as applied to claims 32-34, 36-38, 40, and 46-48 above, and further in view

of Cainelli et al. (Synth. Comm. Pp. 45-47 (1989), provided by Applicant on the IDS dated 1/9/2006).

As discussed above, **Suzuki et al**. (scheme 1) disclose a process for the synthesis of estetrol from estrone, comprising

(1) converting estrone into 3-A-oxy-estra-1,3,5(10),15-tetraen-17-one, wherein A is a protecting group (compound 1b);

(2) reducing the 17-keto group to 3-A-oxy-estra-1,3,5(10),15-tetraen-17β-ol (compound 2a);

(3) protecting the 17-OH group to give 3-A-oxy-17-Cp-oxy-estra-1,3,5(10),15-tetraene, wherein Cp is a protecting group (compound 2b);

(4) oxidizing the carbon-carbon double bond of ring D (C_{15}=C_{16}) to give 3,17-diprotected estetrol (compound 3b);

(5) and removing the protecting groups A and Cp to give estetrol,

as recited by steps 1, 2, 3, 4, and 5 of claim 32.

Suzuki et al. disclose acetyl as the 17-OH protecting group Cp, as recited by claims 32, 35, and 36; reduction of the carbonyl (17-keto) group with a metal hydride compound ($LiAlH_4$), as recited by claims 37 and 38; and oxidation of the Δ^{15} double bond with OsO_4, as recited by claim 40.

Poirier et al. disclose the conversion of estrone to estra-1,3,5(10),15-tetraen-17-one according to well-known methodology (p. 7758), followed by protection of the 3-OH group with benzyl or methyl to give 3-benzyloxy-estra-1,3,5(10),15-tetraen-17-one (compound 8) or 3-methoxy-estra-1,3,5(10),15-tetraen-17-one (compound 9),

respectively (p. 7758; scheme 1). Compound (8) corresponds to the claimed compound wherein protecting group A is a benzyl group, as recited by claims 32-34, and compound (9) corresponds to the claimed compound wherein protecting group A is a methyl (C_1-C_5 alkyl) group, as recited by claim 32.

In addition, Poirier et al. disclose the deprotection of the 3-OH protecting group A, corresponding to step 5 as recited by claim 32. Where the 3-OH protecting group A is benzyl, it can be removed by catalytic hydrogenation at atmospheric pressure using hydrogen gas with a palladium/carbon (Pd/C) catalyst (scheme 1, step (f); p. 7755), as recited by claims 46 and 47. Where the 3-OH protecting group A is methyl, it can be removed by using BBr_3 in dichloromethane (scheme 1, step (g)), as recited by claim 48.

Thus, Poirier et al. teach the protection and deprotection of the 3-OH group of D-ring modified estrogens with a benzyl group or with a methyl group. The 3-O-benzyl- or 3-O-methyl-protected compounds (8) and (9) are disclosed as starting materials for synthesis of C_{15} alkylated steroids, which Poirier et al. carried out by the use of copper-catalyzed conjugate addition of Grignard reagent (p. 7752).

One of ordinary skill in the chemical arts would have been motivated to modify the 3-O-acetate (ester) protecting group disclosed by Suzuki et al. by protecting the 3-OH group with O-methyl or O-benzyl ethers, as taught by Poirier et al., because the following step, reduction with $LiAlH_4$, cleaves the acetate protecting group to yield the unprotected 3-OH (conversion of compound 1b to compound 2a), and requires re-protecting the 3-OH group in the next step (conversion of compound 2a to compound 2b) to survive the reaction conditions of the steps that follow. $LiAlH_4$ is known to reduce

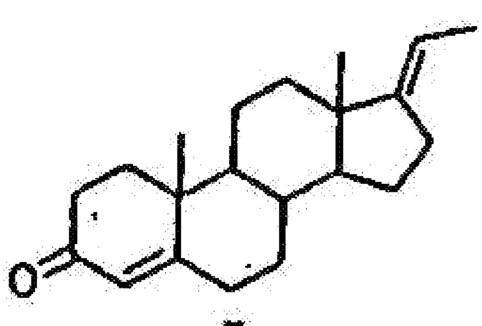
esters (such as –OAc) to primary alcohols, while methyl or benzyl 3-OH protecting groups (ethers) would not be reduced by $LiAlH_4$ (see, e.g., Greene, disclosing that methyl ether and benzyl ether (hydroxyl protecting groups 1 and 26) have low reactivity, i.e., are stable, in the presence of hydride reducing agents including $LiAlH_4$ and $NaBH_4$). Thus, methyl and benzyl ethers would be expected to function as effective 3-OH protecting groups that would obviate the need to subsequently repeat a hydroxyl-protecting step following the metal hydride reduction.

It is noted that Suzuki et al. disclose the simultaneous cleavage of the 3-OAc and 17-OAc protecting groups by alkaline hydrolysis (conversion of compound 3b to compound 3a, estetrol), rather than separate deprotection steps, namely deprotection of the 3-OH group prior to deprotection of the 17-OH group, as recited by claim 32. However, whereas the 3-OH and 17-OH protecting groups of Suzuki are identical (acetate), it is predictable that distinct reagents for each deprotection step may be necessary where the protecting groups are different, as required by the definitions of A and Cp as recited by claim 32. Further, the specification indicates that the order of the deprotection steps can be reversed or performed simultaneously with no material change in the final product (WO04/41839, p. 20, lines 17-26). As recognized by MPEP §2144.04, citing *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946), selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results; see also *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (selection of any order of mixing ingredients is *prima facie* obvious).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the synthesis of estetrol from estrone as taught by Suzuki et al. by modifying the 3-OH protecting group from acetate to methyl or benzyl, as taught by Poirier et al. with a reasonable expectation of success, because doing so would eliminate the need to repeat the 3-OH protecting step, simplifying the process.

However, Suzuki et al. and Poirier et al. do not disclose oxidation of the Δ^{15} double bond with a catalytic amount of OsO_4 immobilized on PVP in combination with trimethylamine-N-oxide, as recited by claims 41-45.

Cainelli et al. disclose a method of catalytic hydroxylation of olefins with catalytic amounts of OsO_4 in combination with trimethylamine-N-oxide, a secondary oxidant which continuously regenerates the tetroxide (p. 45). In addition, Cainelli et al. teach the use of OsO_4 linked to poly-4-vinylpyridine (PVP) in the presence of trimethylamine-N-oxide, which was found to achieve the best results, fast reaction rate, and high yields in the hydroxylation of olefin substrates (p. 46, left column). While not exemplified, Cainelli et al. suggest the utility of OsO_4-PVP/trimethylamine-N-oxide in the *cis*-hydroxylation of steroidal double bonds, such as the 17(20)-double bond of compound 5,



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One of ordinary skill in the chemical arts would have been motivated to modify the oxidizing agent OsO_4 as disclosed by Suzuki et al. by linking it to PVP, employing it with the co-oxidant trimethylamine-N-oxide, and using it in only catalytic amounts, as taught by Cainelli et al., because the modifications taught by Cainelli et al. require less of the expensive and dangerous reagent OsO_4 while improving reaction time and yield (p. 46, right column), and simplifying separation from the reaction medium (p. 45).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the synthesis of estetrol disclosed by Suzuki et al., as modified by Poirier et al., by reducing the Δ^{15} double bond with only catalytic amounts of OsO_4 linked to PVP in the presence of trimethylamine-N-oxide, as taught by Cainelli et al., with a reasonable expectation of success, because OsO_4 was known as the reagent of choice for converting alkenes to *cis*-diols (such as the C_{15}-C_{16} double bond of 3-A-oxy-17-C-oxy-estra-1,3,5(10),15-tetraene), and the modifications disclosed by Cainelli et al. improve safe handling of OsO_4 and achieve better yields of the hydroxylated product.

RESPONSE TO ARGUMENTS

Applicant's arguments filed 9/27/2010 have been fully considered but they are not persuasive. Specifically, Applicant contends that Suzuki's failure to incorporate the earlier-published teachings of Poirier (that is, protecting the 3-OH with benzyl or methyl rather than acetyl) of which Suzuki presumably would have been aware, suggests that

the combination is not obvious (Remarks, p. 7). While the Poirier reference (1991) was indeed published prior to the Suzuki reference (1995), this argument is not material to the legal standard of obviousness under 35 U.S.C. 103.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The scope and contents of the prior art are set forth above. With respect to the differences between the prior art and the claimed invention, the only elements of claim 32 not disclosed by Suzuki et al. are

- an acetyl rather than a C_1-C_5 alkyl or C_7-C_{12} benzylic 3-OH protecting group (A); and
- deprotection of the 3-OH (i.e., removal of (A)) prior to deprotection of the 17-OH (i.e., removal of (Cp)).

With respect to the level of ordinary skill in the chemical arts, in particular synthetic organic chemistry, a skilled artisan would be well aware of a wide range of protecting groups suitable for use under various reaction conditions, such as those set forth in Greene's, a standard industry reference. The art of organic synthesis is largely centers on selecting optimal protecting groups, reagents, and reaction conditions to maximize yield of the final product. Thus, a skilled artisan would regularly engage in

synthesis planning with the goal of using as few steps as possible, since each additional step risks a reduction in the overall yield.

Whether or not Suzuki was aware of Poirier's work is immaterial to the question of obviousness, which inquires into what a hypothetical “person of ordinary skill in the art” would have known at the time then invention was made. Here, the hypothetical skilled artisan would have been aware of the work of Suzuki and Poirier, and, as evidenced by Greene’s, would have been motivated to modify Suzuki in view of Poirier because, as noted above, protecting the 3-O group with benzyl or methyl rather than acyl would eliminate an additional protection step. This would be expected to improve the reaction yield, because it is well-known that some amount of product is lost with each additional protection/deprotection step.

Further, Applicant states that “Suzuki teaches that both the 3-OH and the 17-OH groups are acetylated after the reduction with $LiAlH_4$ (Office Action at pages 10-11). In contrast, claim 32 recites that the 17-OH group is acetylated after the reduction step” (Remarks, p. 8). However, this misstates both the Office Action and Suzuki. To clarify, Suzuki teaches first acetylating the 3-OH group (1a to 1b), followed by reducing the 17-keto group with $LiAlH_4$ (1b to 2a), followed by acetylating the 17-OH group (2a to 2b) (see Scheme 1). This sequence is identical to steps 1, 2, and 3 as recited by claim 32.

In addition, Applicant contends that the claims recite sequentially removing first the 3-O-protecting group followed by removing the 17-O-protecting group (Remarks, p. 8). However, as noted above, the instant specification discloses that the order of the deprotection steps can be reversed or performed simultaneously with no material

change in the final product (WO04/41839, p. 20, lines 17-26). Further, as recognized by MPEP §2144.04, selection of any order of performing process steps is *prima facie* obvious in the absence of new or unexpected results (see *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946); and *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930) (selection of any order of mixing ingredients is *prima facie* obvious)).

Applicant further contends that the Examiner offers no motivation to modify the 3-O protecting group (that is, by protecting the 3-OH with benzyl or methyl rather than acetyl) (Remarks, p. 8). However, the secondary and evidentiary references provide the motivation to modify Suzuki. Specifically, Poirier et al. teach the protection and deprotection of the 3-OH group of D-ring modified estrogens with a benzyl or methyl group. In addition, Pearlman discloses that acyl or benzyl protecting groups can be used equivalently where $NaBH_4$ is the reducing agent. Greene's, a standard organic chemistry reference, confirms that methyl ether and benzyl ether are stable hydroxyl protecting groups in the presence of hydride reducing agents including $LiAlH_4$ and $NaBH_4$. Thus, as detailed above, it would have been predictable to a skilled artisan that the reaction could be successfully carried out when modifying the 3-O-acetyl protecting group taught by Suzuki to a 3-O-benzyl or 3-O-methyl protecting group taught by Poirier, with the advantage of eliminating a protection/deprotection step, which would be expected to improve the overall yield.

Thus, the rationale to combine the references is premised on the findings that (1) the prior art includes each element claimed, with the only difference between the claimed invention and the prior art being the lack of actual combination of the elements

in a single prior art reference; (2) one of ordinary skill in the art could have combined the elements as claimed by known methods, and that in combination, each element merely performs the same function as it does separately; and (3) one of ordinary skill in the art would have recognized that the results of the combination were predictable.

With respect to the fourth Graham factor, evidence of secondary considerations, Applicant contends that evidence of unexpected results disclosed in the specification, namely 10% yield in comparison to 8% achieved by Suzuki, is sufficient to overcome a *prima facie* case of obviousness (Remarks, p. 8). However, the passage cited (p. 6, lines 5-9) is not experimental data, but rather a hypothetical result: "By a good yield, it is meant a yield of at least 10%, preferably higher than 10%, more preferably of at least 12.5%, starting from estrone (100%)." For the reasons set forth above, a skilled artisan would expect at least this small (approx. 2%) increase in yield.

As recognized by MPEP §2143, combining prior art elements according to known methods to yield predictable results would motivate the skilled artisan to modify the references with a reasonable expectation of success. The rationale to support a conclusion of *prima facie* obviousness is that all the claimed elements were known in the prior art, and a skilled artisan could have combined the elements as claimed by known methods with no change in their respective functions, and the combination yielded nothing more than predictable results to one of ordinary skill in the art. See *KSR Int'l Co. v. Teleflex Inc.* (550 U.S. 398, 409).

CONCLUSION

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

CORRESPONDENCE

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SARA E. CLARK whose telephone number is (571) 270-7672. The examiner can normally be reached on Mon - Fri, 8:30 am - 5:00 pm (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian-Yong Kwon, can be reached at 571-272-0581. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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